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Ambient Water Quality Criteria Document
Addendum for Chlordane

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ADDENDUM FOR CHLORDANE

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OFFICE OF WATER REGULATIONS
AND STANDARDS

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PREFACE

Under the 1977 Clean Water Act, Congress mandated the U.S. Environmental Protection Agency to develop ambient water quality criteria for 129 priority pollutants. These criteria were published in 1980. Under Section 304(a)(1) of the Clean Water Act as amended in 1987, the U.S. EPA is mandated to re-evaluate and update these criteria every five years. These addenda represent an updated literature search current as of 1988, plus additional information from Agency files and Program Offices. The first draft of this addendum was prepared by Syracuse Research Corporation under contract no. 68-C8-0004.

TABLE OF CONTENTS

	<u>Page</u>
INTRODUCTION	1
REVIEW OF NEW DATA	4
Toxicologic/Carcinogenic Effects	4
Bioconcentration Factor (BCF).	7
QUANTIFICATION OF EFFECTS.	8
EXISTING STANDARDS AND CRITERIA.	10
REFERENCES	12

LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
bw	Body weight
CRAVE	Carcinogen Risk Assessment Verification Endeavor
DWEL	Drinking water equivalent level
HA	Health advisory
LOAEL	Lowest-observed-adverse-effect level
MCLG	Maximum contaminant level goal
NOAEL	No-observed-adverse-effect level
PEL	Permissible exposure limit
ppm	Parts per million
RfD	Reference dose
RQ	Reportable quantity
TLV	Threshold limit value
TWA	Time-weighted average

INTRODUCTION

Under Section 304(a)(1) of the Clean Water Act of 1977 as amended in 1987, the U.S. EPA is required to publish criteria for water quality accurately reflecting the latest scientific knowledge regarding the effects on health and welfare that may occur from the presence of pollutants in any body of water, including groundwater. In accordance with the 1977 act, Ambient Water Quality Criteria Documents (AWQCDs) were developed in 1980 for 65 toxic pollutants or classes of pollutants listed under Section 307(a)(1).

These addenda are intended to serve as an update of the original AWQCDs. The addenda provide the Agency with the latest scientific assessments of potential health hazards associated with these pollutants and serve as guidelines for modifying the current (1980) AWQCDs.

The human health criteria in these addenda are based on Agency verified risk assessment values when available. These values consist of reference doses (RfD) for those chemicals believed to be systemic toxicants (i.e., do not induce cancer) and cancer risk factors for those thought likely to cause cancer in humans. The verification process consists of a review and consensus of risk assessment values provided by an Agency workgroup consisting of scientists from each of the major Agency offices. Assessments for noncarcinogens are verified by the RfD workgroup and those for carcinogens are verified by the Carcinogen Risk Assessment Verification Endeavor (CRAVE) workgroup. If such values are not available, the criteria are based on the most recent Agency health assessment. In the absence of any appropriate Agency value, RfD values or cancer risk factors are derived by current Agency methods if adequate new data are available, and criteria are recommended based on the proposed RfD or risk factor.

The RFD is an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RFD is derived by dividing a NOAEL or LOAEL for subchronic or chronic exposure by standard uncertainty factor(s) times an additional uncertainty factor:

$$RFD = \frac{NOAEL \text{ or } LOAEL}{UF(s) \times UF}$$

The standard uncertainty factors are applied to reflect the various types of data used to estimate RFDs. An uncertainty factor of 10 is used to account for variations in human sensitivity when extrapolating from valid human studies involving long-term exposure of average, healthy subjects. An additional 10-fold factor is used for each of the following: to extrapolate from long-term animal studies to the case of humans, to extrapolate from subchronic animal studies to chronic exposure, and to extrapolate from a LOAEL to a NOAEL. An additional uncertainty factor of >0-10 may be applied to reflect professional assessment of the uncertainties of the study and data base not explicitly addressed by the standard uncertainty factors (i.e., completeness of the overall data base). The default value for the additional uncertainty factor is 1.

In assessing the carcinogenic potential of a chemical, the U.S. EPA classifies the chemical into one of the following groups according to the degree of evidence in epidemiological studies and animal studies: Group A - Human Carcinogen; Group B - Probable Human Carcinogen [limited evidence in humans with or without sufficient evidence in animals (Group B1) or inadequate evidence in humans with sufficient evidence in animals (Group B2)]; Group C - Possible Human Carcinogen (limited evidence of carcinogenicity in animals in the absence of human data); Group D - Not Classifiable as to

Human Carcinogenicity (Inadequate or no evidence); Group E - Evidence of Noncarcinogenicity for Humans. Quantitative carcinogenic risk assessments are performed for chemicals in Groups A and B, and on a case-by-case basis for chemicals in Group C. Upper-bound cancer unit risks (slope values) are estimated through the use of mathematical extrapolation models. Most commonly for animal data, the linearized multistage model with a 95% upper confidence limit is used to provide a low-dose estimate of cancer risk. The cancer risk is characterized as an upper-limit estimate (i.e., the true risk to humans, while not identifiable, is not likely to exceed the upper-limit estimate and in fact may be lower). Alternative risk models to the multistage model, such as the one-hit, Weibull, Logit or Probit model, are available and may be used when the evidence indicates that they may be more appropriate. In the absence of such evidence, the Agency recommends the linearized multistage model to provide consistency of approach and an upper-bound on the potential carcinogenic risk. In the case where human data are used for quantitative risk assessment, an upper-bound estimate rather than a 95% upper-bound estimate is used when low-dose linearity is assumed.

In the development of this Addendum to the AWQCD on chlordane, recent Agency assessments have been consulted. A computerized literature search was conducted to cover studies published more recently than the latest Agency assessment (i.e., published in 1987 to 1988). New key studies have been evaluated.

REVIEW OF NEW DATA

Toxicologic/Carcinogenic Effects

The ambient water quality criteria for chlordane are based on animal carcinogenicity data (see next section). U.S. EPA (1986, 1987a) judged human carcinogenicity data to be inadequate for qualitative or quantitative assessment. Three epidemiology studies of pesticide applicators or manufacturing workers reported negative or marginally positive results for cancer mortality, but were confounded by exposure to other chemicals or were inadequate because of sample size and duration of follow-up (U.S. EPA, 1986, 1987a). The U.S. EPA (1987a) cited 11 case reports from Infante et al. (1978) that reportedly involved blood dyscrasias, neuroblastomas and central nervous system effects in children exposed pre- and postnatally to chlordane.

A more recent study by Epstein and Ozonoff (1987) not mentioned in U.S. EPA (1987a), reported 25 previously unpublished cases of blood dyscrasia among persons whose homes were treated for termites with the chlorinated hydrocarbon pesticides chlordane and heptachlor. The blood dyscrasias included leukemias, aplastic and pernicious anemias and thrombocytopenic purpura, consistent with 34 published cases (Epstein and Ozonoff, 1987), including those presented by Infante et al. (1978) as mentioned above. The case reports by Infante et al. (1978) and Epstein and Ozonoff (1987) provided insufficient information to base conclusions on the carcinogenicity of chlordane in humans; therefore, the evidence of carcinogenicity for humans remains inadequate.

Four mouse and four rat carcinogenesis bioassays were reviewed by U.S. EPA (1987a) and constitute a sufficient animal data base for carcinogenicity risk assessment. Of the four studies in rats, only one provided positive

evidence of carcinogenicity (U.S. EPA, 1987a). A significant increase in hepatic adenomas was found in male F344 rats at the highest dose tested in a 130-week dietary study (RIASBT, 1983a).

Positive results for carcinogenicity were reported in all four mouse bioassays (U.S. EPA, 1987a). Because the quantitative risk assessment was based on data for the mouse (the more sensitive species), it is the mouse studies that are described here. Becker and Sell (1979) fed a 90:10 mixture of chlordane/heptachlor to an unspecified number of C57B1/6N mice (a strain that has not been known historically to develop spontaneous liver tumors). Dose levels of 0, 25 and 50 ppm (0, 3.57 and 7.14 mg/kg bw) were administered in the diet for 18 months. None of 200 control mice developed liver tumors or nodular lesions, while 27% (16) of the surviving treated mice had primary hepatocellular carcinomas, first appearing at age 36 weeks. Other pertinent details of this study were not available.

Epstein (1976) described a study done by IRDC (1973) and its reevaluation by Reuber (Epstein, 1976). IRDC (1973) exposed groups of 100 male and 100 female CD-1 mice (6 weeks old) to diets containing 0, 5, 25 or 50 ppm analytical grade chlordane for 18 months, at which time survivors were killed. IRDC (1973) reported a significant dose-related increase ($p < 0.01$) at 25 and 50 ppm in nodular hyperplasias in livers of both sexes. In a reevaluation of the slides from this study, Reuber (Epstein, 1976) reported a high incidence of hepatic carcinomas instead of hyperplastic nodules at 25 and 50 ppm. Other pathologists who reevaluated the slides agreed substantially with Reuber's diagnoses (Epstein, 1976). The incidences from Reuber's reevaluation, as reported in Epstein (1976), were used in quantitative risk assessment (see next section).

NCI (1977) fed two groups each of 50 male and 50 female B6C3F1 mice technical-grade chlordane (94.8% purity) in the diet for 80 weeks at TWA concentrations of 29.9 and 56.2 ppm (males) and 30.1 and 63.8 ppm (females); survivors were killed at ~90 weeks. Matched controls consisted of 20 male and 20 female mice. A dose-related increase in hepatocellular carcinomas was observed in both sexes ($p < 0.001$).

RIASBT (1983b) fed technical grade chlordane to groups of 80 male and 80 female ICR mice in the diet at 0, 1, 5 or 12.5 ppm for 24 months. The highest-dosed group of males developed a statistically significant ($p < 0.05$) increase in the incidence of hepatocellular adenomas and hemangiomas of the liver, but no increase in hepatic tumors was found in females.

Based on inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in animals (both sexes of four strains of mice and in F344 male rats), chlordane is classified in U.S. EPA Group B2 - probable human carcinogen (U.S. EPA, 1987a,b). It was noted that chlordane is structurally related to other known liver carcinogens (e.g., aldrin, dieldrin, heptachlor).

The U.S. EPA (1989) has verified an oral RFD of 6×10^{-5} mg/kg/day, based on a NOEL of 0.055 mg/kg/day (1 ppm diet) from a chronic rat study conducted for Velsicol Chemical Corporation (RIASBT, 1983a). F-344 rats (80/sex/dose) were fed technical-grade chlordane at dose levels of 0, 1, 5 or 25 ppm for 130 weeks. Body weight, food consumption, water intake, hematology, clinical chemistry, urinalysis and gross and microscopic pathology endpoints were examined. A NOEL for liver lesions in female rats was identified at the 1 ppm dietary level. An uncertainty factor (UF) of 100 was used to account for the inter- and intraspecies differences. An additional UF of 10 was used to account for the lack of an adequate

reproduction study and adequate chronic study in a second mammalian species, and the generally inadequate sensitive endpoints studied in existing studies, particularly since chlordane is known to bioaccumulate over a chronic duration.

Bioconcentration Factor (BCF)

Pertinent new information concerning the bioconcentration factor for chlordane is currently undergoing Agency review. The BCF value of 14,100 determined in U.S. EPA (1980) will be used until this review is completed.

QUANTIFICATION OF EFFECTS

The ambient water criteria derived for chlordane were 0.046, 0.46 and 4.6 ng/l, corresponding to lifetime increased cancer risk levels of 10^{-7} , 10^{-6} and 10^{-5} , respectively. The criteria were calculated from a q_1^* (slope factor) of $1.6075 \text{ (mg/kg/day)}^{-1}$, assuming a daily intake of 2 l of drinking water, consumption of 6.5 g fish and shellfish with a BCF for chlordane of 14,100 and a 70 kg body weight (U.S. EPA, 1980). The slope factor was based upon incidences of liver carcinomas in male CD-1 mice in the IRDC lifetime study of chlordane in the diet (IRDC, 1973; Reuber re-evaluation in Epstein, 1976).

A new slope factor of $1.3 \text{ (mg/kg/day)}^{-1}$ has been estimated by the U.S. EPA (1986, 1987a,b) and verified by the Agency-wide CRAVE committee (U.S. EPA, 1987a). The corresponding drinking water unit risk factor is $3.7 \times 10^{-5} / \mu\text{g/l}$ (U.S. EPA, 1987a). The verified slope factor represents the geometric mean of slope factors from four data sets showing significant increases in the incidence of hepatocellular carcinomas in mice. The four slope factors are 4.74 and $2.98 \text{ (mg/kg/day)}^{-1}$ for male and female CD-1 mice, respectively (IRDC, 1973; Epstein, 1976) and 0.76 and $0.25 \text{ (mg/kg/day)}^{-1}$ for male and female B6C3F1 mice, respectively (NCI, 1977).

Quantification of new ambient water criteria for chlordane using the verified slope factor is appropriate, since this value incorporates a wider and more adequate data base. Using the slope factor of $1.3 \text{ (mg/kg/day)}^{-1}$ (U.S. EPA, 1987a), and assuming a 70 kg body weight and a daily intake of 2 l of water and 6.5 g fish and shellfish with a BCF of 14,100, ambient water quality criteria are estimated as follows:

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (ng/l)				
	0	10^{-7}	10^{-6}	10^{-5}	10^{-4}
2 % of drinking water and consumption of 6.5 g of fish and shellfish	0	0.057	0.57	5.7	57
Consumption of fish and shellfish only	0	0.059	0.59	5.9	59

EXISTING STANDARDS AND CRITERIA

The Health Advisory Program of the Office of Drinking Water has established a 10-day HA for a child of 0.06 mg/l. Insufficient data exist for establishment of a 1-day or longer-term HA for a child, but it is recommended that the 10-day HA of 0.06 mg/l be used as the 1-day HA, and that the modified DWEL (adjusted for a 10 kg child) of 0.5 µg/l serve as the longer-term HA. Sufficient data for calculating a longer-term HA for adults are lacking also, and it is recommended that the DWEL of 2 µg/l, adjusted for the 70 kg adult, be used as such. No lifetime HA has been accepted (U.S. EPA, 1989).

The MCLG for chlordane in drinking water is 0 mg/l, proposed in 1985. This is based on its carcinogenic effects, but does not consider technological or economic feasibility (U.S. EPA, 1989).

WHO (1984) set a drinking water guideline at 0.3 µg/l. FAO/WHO (1984) reported a recommended ADI of 1 µg/kg bw for chlordane, and NRC (1982) recommended an interim guideline of 5 µg/m³ for chlordane in air in military housing facilities.

OSHA (1985) has established a PEL of 0.5 mg/m³. This corresponds to the TLV-TWA of 0.5 mg/m³ in air adopted by the ACGIH (1987). Both agencies note that chlordane can be absorbed through the skin.

Use of chlordane as a pesticide was disapproved in 1987 under Special Review, Federal Insecticide and Rodenticide Act, with a few exceptions. Uses not affected by this decision or previous suspension were: 1) sub-surface application for termite control; 2) treatment of nonfood roots and tops (U.S. EPA, 1989).

The RQ for release into the environment is 1 pound (proposed, 1987), based on aquatic data (U.S. EPA, 1989).

The verified oral slope factor for chlordane is $1.3 \text{ (mg/kg/day)}^{-1}$, the drinking water unit risk factor is $3.7 \times 10^{-5} / \mu\text{g/l}$, and the oral RfD is $6 \times 10^{-5} \text{ mg/kg/day}$ (U.S. EPA, 1987a, 1989).

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